

REMARKS/ARGUMENTS

After entry of this amendment, claims 1, 4, 7, 9, 11-17 and 26-30 are pending, of which claim 27 is withdrawn. The claims have been amended without prejudice or disclaimer and find support *inter alia* in the original claims. Claim 4 finds further support in the specification, for example, at page 17, line 15 through page 18, line 16, and at page 44, line 32 through page 45, line 3. No new matter has been added.

Finality of the Present Action

Applicants respectfully request that the finality of the present action be withdrawn, because the finality of the present Office Action is inappropriate for at least the following three reasons.

First, the Examiner has indicated a new grounds for rejection under anticipation. Specifically, the Examiner states at page 6 of the Office Action “***New-Claim Rejections*** – 35 U.S.C. § 102.” (emphasis added). Claims 29-30 were not previously rejected. The Examiner himself indicates that this is a new rejection.

Second, the Examiner has indicated second new grounds for rejection under obviousness. Specifically, the Examiner states at page 7 of the Office Action “***New-Claim Rejections*** – 35 U.S.C. § 103.” (emphasis added). Claim 11 (at pages 8-9) and claims 1, 7, 9, 12-17, 26, and 28 (at pages 10-11) were not rejected under this rejection in the previous office action. The Examiner himself indicates that this is a new rejection.

Finally, the Examiner in the obviousness rejection in the Final Office Action cites a new reference, *i.e.* Allen *et al.*, to support the rejection. Pursuant to MPEP § 706.07(a), a second or any subsequent action on the merits in any application will not be made final if it includes a rejection, on newly cited art. Because this is a new reference to support the obviousness rejection, the action should not have been made final.

Because new grounds for rejection were included in the final Office Action as also acknowledged by the Examiner and new references were cited, the present action should not

have been made final. Applicants respectfully request that the finality of the Office Action dated June 9, 2010, be reconsidered and withdrawn.

Because of the finality of the Office Action, the filing of a Request for Continued Examination accompanying this response was necessitated. Should the finality of the action be withdrawn as it should, Applicants request a refund of the fee associated with the filing of the Request for Continued Examination.

Rejections under 35 U.S.C. § 112

Claim 4 was rejected under 35 U.S.C. 112, first paragraph, for alleged lack of an enabling disclosure. Applicants respectfully disagree and traverse the rejection.

The Examiner alleges that “the disclosure is limited to the nucleotide and encoded amino acid sequence of only one lysine degrading protein i.e. threonine aldolase of SEQ ID NO: 12 encoded by SE ID NO: 11.” Applicants strongly disagree.

The specification discloses not just one but six lysine decarboxylase or lysine decarboxylase-like protein, i.e. SEQ ID NO: 12, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, or SEQ ID NO: 26, and their encoding nucleic acids, i.e. SEQ ID NO: 11, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 25. (Specification, for example, at page 17, line 15 through page 18, line 16).

Moreover, Applicants further note that conserved residues between various lysine decarboxylases are provided, for example, in Figure 2 of the present application. Thus, the requisite guidance is further provided in the specification because, based on the alignment, one skilled in the art would be able to ascertain where substitutions could or should not be made.

Nonetheless, in order to expedite prosecution, claim 4 has been amended without prejudice or disclaimer and recites specific sequences from which the consensus sequence had been obtained.

Furthermore, the specification provides detailed guidance on how to make the nucleic acids as claimed and following this teaching has provided at least six sequences which fall within

the scope of the claims. Additionally, the specification discloses the activity of the polynucleotides and polypeptides and provides detailed guidance on how to screen and test for activity. Thus, the detailed guidance provided in the present specification and the routine nature of the screening for the claimed activity overcome the unpredictability alleged by the Examiner.

Further even if we were to assume that the amount of experimentation to practice the full scope of the claimed invention might be extensive, such experimentation would have been routine. The specification provides detailed screening and assays to determine activity of the sequences. The methods for performing such screening and plant transformation were also well known to those skilled in the art. *See, e.g., Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) (“test [for undue experimentation] is not merely quantitative ... if it is merely routine”). Under the applicable law, the test for “undue experimentation” is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Ex parte Jackson*, 217 USPQ 804, 807 (1982); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

For at least the above reasons and for the reasons already of record, reconsideration and withdrawal of the rejection is respectfully requested in view of the present amendments.

New Rejections under 35 U.S.C. § 102

Claims 29 and 30 were rejected for the first time under 35 U.S.C. § 102 (b) as allegedly being anticipated by Monschau *et al.* (hereinafter “Monschau”).

The Examiner asserts that Monschau teaches “a method of producing L-amino acid glycine in a fungal strain *Ashbya gossypii* comprising overexpressing a gene encoding threonine aldolase from *S. cerevisiae*, which degrade threonine, which is 99.8% identical to SEQ ID NO: 2, inherently a threonine degrading enzyme.” (Final Office Action dated June 9, 2010, page 7). Applicants strongly disagree with the Examiner’s characterization of the Monschau reference and traverse the rejection.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegall Bros., Inc. v.*

Union Oil Co., 814 F.2d 628, 631 (Fed. Cir. 1987). “Rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention. The prior art reference must **clearly and unequivocally** disclose the claimed invention or direct those skilled in the art to the invention without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.” *Net MoneyIN Inc. v. VeriSign Inc.*, 545 F.3d 1359 (Fed. Cir. 2008) (holding “that unless a reference discloses within the four corners of the document not only all the limitations claimed but also **all of the limitations arranged or combined in the same way** as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.”) (emphasis added).

Monschau differs from the present claims in at least the four following ways:

First, Monschau discloses throughout that it is **the GLYI gene of *A. gossypii*** that was isolated, characterized, and overexpressed as explained in detail in the previous response (see Amendment and Reply Under 37 CFR 1.111 dated March 15, 2010, page 8). Monschau teaches the overexpression of the *GLYI* gene of *A. gossypii* in *A. gossypii*. The *GLYI* gene of *A. gossypii* was also expressed in the glycine autotrophic strain YM13.

Second, Monschau does not teach overexpressing the threonine aldolase gene from *S. cerevisiae*. The only occasion where the *GLYI* gene of *S. cerevisiae* is mentioned in Monschau is when the deduced amino acid sequence of the *GLYI* gene of *A. gossypii* is compared with that of the *GLYI* gene of *S. cerevisiae*. (Monschau at page 4285, paragraph bridging left and right Cols).

Third, the sequence used by Monschau for producing L-amino acid glycine is **the GLYI gene of *A. gossypii*** which, according to Monschau, **shares 88% SIMILARITY** with the *GLYI* gene of *S. cerevisiae*. The percent identity with the sequence used by Monschau would thus be substantially lower.

Fourth, the *GLY1* gene of *A. gossypii* used in Monschau shares only **66% sequence identity with SEQ ID NO: 1** of the present application based on ClustalW alignment program using default parameters. Even the deduced amino acid sequence of the *GLY1* gene of *A. gossypii* shares only **75% sequence identity with SEQ ID NO: 2** of the present application. Thus, Monschau does **NOT** teach overexpressing a threonine aldolase gene having 99.8% identity to SEQ ID NO: 2 as alleged by the Examiner, or a nucleotide sequence encoding a polypeptide having at least 95% identity to SEQ ID NO: 2 as recited in the claims.

Because Monschau does not teach all of the limitations arranged or combined in the same way as recited in the claim, a *prima facie* case of anticipation has not been established and the rejection should be withdrawn. Reconsideration and withdrawal of the rejection is respectfully requested.

New Rejections under 35 U.S.C. § 103

Claim 11 was newly rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Monschau in view of Allen *et al.* (hereinafter "Allen"). Applicants respectfully disagree and traverse the rejection.

As an initial matter, claim 11 is a dependent claim, which depends from claim 29. Since independent claim 29 has not been rejected for obviousness, then claim 11, which depends therefrom, is likewise not obvious. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious). The rejection of claim 11 is therefore improper.

The premise of the Examiner's obviousness argument is that Monschau teaches overexpressing a gene encoding threonine aldolase from *S. cerevisiae* for producing L-amino acid glycine. (Final Office Action dated June 9, 2010, p. 7). However, the disclosure of Monschau does not support this position, which renders the rejection clearly erroneous.

Applicants respectfully remind the Examiner that it is the Examiner who bears the initial burden of establishing *prima facie* obviousness. *See In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or

suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994); see also *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341 (Fed. Cir. 2008) (“[t]he KSR opinion ... did not mention or affect the requirement that each and every claim limitation be found present in the combination of the prior art references before the analysis proceeds.” (emphasis added) (quoting *Abbott Labs. v. Sandoz, Inc.*, 500 F.Supp.2d 846, 852 (N.D.Ill. 2007))). Moreover, it is well established that under 35 U.S.C. § 103 the Examiner must consider the reference in its entirety, *i.e.* as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

As explained above under the anticipation rejection, the arguments of which are equally applicable here and hereby incorporated by reference, Monschau does not teach or suggest production of methionine, homoserine, or lysine in a transgenic microorganism by introducing the nucleotide sequence of SEQ ID NO: 1 or a nucleic acid encoding SEQ ID NO: 2 or variant thereof as presently claimed. As explained above, the sequence used by Monschau was the *GLY1* gene of *A. gossypii* which shares only 66% sequence identity with SEQ ID NO: 1 and only 75% sequence identity with SEQ ID NO: 2. Accordingly, under the correct standard, when considering Monschau in its entirety, Monschau does not teach overexpressing the nucleic acid as claimed.

Further as acknowledged by the Examiner, Monschau does not teach the use of *E. coli* as a host cell for overexpression of a threonine aldolase gene. The Examiner relies on Allen for allegedly teaching a transformed *E. coli* overexpressing a threonine aldolase gene.

However, Allen does not remedy the deficiencies of Monschau.

Allen relates *inter alia* (i) to isolated polynucleotides encoding at least a portion of a glycine metabolism enzyme selected from choline oxidase, L-allo-threonine aldolase, phosphoserine-phosphatase and sarcosine oxidase, (ii) to the construction of chimeric genes encoding all or a portion of the glycine metabolism enzyme, and (iii) to the expression of said chimeric genes resulting in the production of altered levels of said glycine metabolism enzyme in a transformed host cell. (Allen, abstract). The allo-threonine aldolases disclosed in Allen (Table 1D; SEQ ID NO. 16, 18, 20, 22, 38, 40 and 42) share less than about 46 % (GAP) / 48 % (Bestfit) identity with SEQ

ID NO: 2 of the present invention (see attached alignments for each of the Allen sequences of Table 1D compared with SEQ ID NO: 2 of the present claims).

Specifically, SEQ ID NO: 16 is 26.9% based on GAP or 28.3% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 18 is 31.3% based on GAP or 33.6% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 20 is 46.2% based on GAP or 47.6% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 22 is 34.7% based on GAP or 35.5% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 38 is 31.0% based on GAP or 32.4% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 40 is 34.7% based on GAP or 35.3% based on Bestfit identical to SEQ ID NO: 2. SEQ ID NO: 42 is 34.0% based on GAP or 38.1% based on Bestfit identical to SEQ ID NO: 2. Accordingly, as with Monschau, Allen does not teach the nucleotide sequence of SEQ ID NO: 1 or a nucleic acid encoding SEQ ID NO: 2 or variant thereof as in the presently claimed process.

Furthermore, Allen does not disclose the effect of overexpression of the L-allo-threonine aldolase sequences they disclose. Allen does not give any hint of a process for the production of methionine, homoserine and/or lysine.

Thus the combined teachings of Monschau and Allen do not disclose the production of methionine, homoserine, or lysine in a transgenic microorganism by introducing the nucleotide sequence of SEQ ID NO: 1 or a nucleic acid encoding SEQ ID NO: 2 or variant thereof as presently claimed.

Because the combined teaching of the references cited by the Examiner does not disclose or suggest all the claim limitations, a *prima facie* case of obviousness has not been established. For this reason alone, the obviousness rejection should be reversed.

The Examiner further alleges that

“it would have been obvious to one of ordinary skill in the art at the time of the invention was made to use a *E. coli* instead of fungal strain *Ashbya gossypii* as a host cell to express said threonine aldolase gene as taught by Allen et al. and use the method of producing L-amino acid as taught by Monschau et al. to arrive at the claimed invention.” (Office Action date June 9, 2010, page 9).

The Examiner appears to be using the rationale of substituting one organism for another to allegedly arrive at the claimed invention.

As explained in the 2010 *KSR* Guideline Update, “the substitution rationale applies when the claimed invention can be viewed as resulting from substituting a known element for an element of a prior art invention. The rationale applies when one of ordinary skill in the art would have been technologically capable of making the substitution, and ***the result obtained would have been predictable***. See MPEP § 2143(B).” 75 Fed. Reg. 53649 (September 1, 2010). Moreover, in *KSR*, the Supreme Court stated that the “. . . combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” The MPEP at § 2143 has formulated seven exemplary rationales that may be used to support a conclusion of obviousness in accordance with *KSR*. Fundamental to *KSR* and each of the MPEP rationales is the premise that the prior art disclose known methods that ***yield predictable results***.

Moreover, **obviousness cannot be predicated on what is unknown**. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). As found by the court in *In re Antonie*, which reversed the Board’s finding of obviousness, it is the invention as a whole, and not some part of it, which must be obvious under 35 U.S.C.S. § 103. *In re Antonie*, 559 F.2d 618, 619-620 (CCPA 1977); see also MPEP § 2141.02 V. Furthermore, the court in *In re Antonie* found that the prior art did not reveal the property which appellant discovered and, therefore, there was no basis to find obviousness. *Id.* See also *In re Naylor*, 369 F.2d 765, 768 (CCPA 1966) (reversing the Board’s finding of obviousness and holding that one skilled in the art ***must have recognized*** the claimed property would have been the inevitable result of obvious modification.).

It is Applicants position that the claimed process for preparing methionine, homoserine and/or lysine in a transgenic using SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof would not have been predictable from the references cited.

Nothing in Monschau and/or Allen would lead one skilled in the art to expect that overexpression a nucleic acid encoding a threonine degrading protein such as SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof in a microorganism or plant could be used for

preparing methionine, homoserine and/or lysine, especially since Monschau and/or Allen disclose using different genes from different organisms which have low homology to the ones claimed and do not mention production of methionine, homoserine and/or lysine.

Because Monschau and Allen do not teach, suggest or even mention overexpression of SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof, there is no basis for finding obviousness.

Moreover, analogous to *In re Antonie*, neither Monschau nor Allen recognized or predicted that expression of SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof influences production of methionine, homoserine and/or lysine. See MPEP § 2143 (If any of the findings cannot be made (*i.e.* the substitution of one known element for another yielding predictable results to one of ordinary skill in the art), then the rationale on which the Examiner based the obviousness rejection cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art); *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007).

Furthermore, since nothing in Monschau and Allen directs one skilled in the art to produce methionine, homoserine and/or lysine using a transgenic microorganism or plant comprising and expressing SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof, the teachings of Monschau and Allen do not teach or suggest making any modification that would result in a transformed plant or microorganism for use in preparing methionine, homoserine and/or lysine as claimed. Accordingly, Monschau and Allen do not render the claims obvious. See *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990) (The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification).

Further even assuming *arguendo* that the organisms were substitutable, the combined teaching of the references still does not arrive at the claimed invention, since Monschau and Allen do not teach overexpression of SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof or production of methionine, homoserine and/or lysine.

Claims 1, 7, 9, 12-17, 26, and 28 were also rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Monschau in view of Allen. Applicants respectfully disagree and traverse the rejection.

The Examiner in this rejection relies on Allen for allegedly teaching a plant cell transformed and overexpressing threonine aldolase gene involved in glycine synthesis. (Office Action dated June 9, 2010, page 10). It appears that the only difference in basis of this rejection is the substitution of organisms being with a plant rather than with *E. coli* as applied to claim 11.

All the arguments presented above for claim 11 are equally applicable here and hereby incorporated by reference.

For all the same reasons as explained above, because Monschau and Allen do not teach, suggest or even mention overexpression of SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof, there is no basis for finding obviousness. The references do not teach or suggest all the claim limitations and further the claimed process for preparing methionine, homoserine and/or lysine in a transgenic using SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof would not have been predictable from the references cited. Accordingly, a *prima facie* case of obviousness has not been established under the correct standard as established in *KSR*.

Further even assuming *arguendo* that the organisms were substitutable, the combined teaching of the references still does not arrive at the claimed invention, since Monschau and Allen do not teach overexpression of SEQ ID NO: 1 encoding SEQ ID NO: 2 or variants thereof or production of methionine, homoserine and/or lysine.

For at least these reasons, withdrawal of the obviousness rejection is respectfully requested for the independent claims and the claims dependent therefrom. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious).

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all the rejections contained in the Office Action dated June 9, 2010 have been addressed and that the application is in condition for allowance or appeal. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

PETITION FOR THREE-MONTH EXTENSION OF TIME

Accompanying this response is a petition for a three-month extension of time to and including December 9, 2010, to respond to the Office action mailed June 9, 2010, and accompanied by the fee required under 37 CFR 1.17(a)(3) and a Request for Continued Examination with the required fees, which are paid herewith by credit card. No additional fee is believed due. However, if any additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 13195-00006-US, from which the undersigned is authorized to draw.

Respectfully submitted,

By 

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Attachments: Alignments between SEQ ID NO: 2 and the sequences from Table 1D of Allen *et al.*

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 16
- US 2002/0123118

GAP of: check: 4547 from: 1 to: 387

readseq-25530_tmp_1 387 bp

to: check: 6869 from: 1 to: 116

readseq-1697_tmp_1 116 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	110	Length:	388
Ratio:	0.948	Gaps:	2
Percent Similarity:	40.870	Percent Identity:	26.957

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
1 .....DPTAR 5
51 RLEQTVARMAGKEAGLFCVSGTSLNQIAIRTH.LMQPPYSILCDYRAHVY 99
|::.:|||:|:::|..::.:|::
6 RFQEEMAALMGKEAALFVPSGTMGNXVSVLAHCXVRGSXQVILGDDSHIH 55
100 THEAAGLAILSQAMVVPVPSNGDYLTLEDIKSHYVPDDGDIHGAPTRLI 149
:|:|:|..|..:|:|:|:|:|:|
56 LYENGGISTLGGVHPKTVRNNSXGTMDDISIVXAIRPPGGGXYYPTTRLI 105
150 SLENTLHGIVYPLEELVRIKAWCMENGLKLHCDGARIWNAAAQSGVPLKQ 199
|||
106 CLEXT.HGNXGG..... 116

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Comparison of SEQ ID NO 2 - present application version SEQ ID NO 16
 - US 2002/0123118

BESTFIT of: 17539.seq1.fas check: 4547 from: 1 to: 387

readseq-8670_tmp_1 387 bp

to: 17539.seq2.fas check: 6869 from: 1 to: 116

readseq-27856_tmp_1 116 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
 CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	119	Length:	108
Ratio:	1.112	Gaps:	2
Percent Similarity:	43.396	Percent Identity:	28.302

Match display thresholds for the alignment(s):

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| = IDENTITY
: = 2
. = 1

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51 RLEQTVARMAGKEAGLFCVSGTLSNQIAIRTH.LMQPPYSILCDYRAHVY 99
| :: .| : ||| || |||: | :: | .. :: .|::
6 RFQEEMAALMGKEAALFVPSGTMGNXVSVLAHCXVRGSXQVILGDDSHIH 55
THEAAGLAILSQAMVVPVPSNGDYLTLEDIKSHYVPDDGDIHGAPTRLI 149
:| |:. | | .. : :: | | : |||
56 LYENGGISLGGVHPKTVRNNSXGTMDIDSIVXAIRPPGGGXYYPTTRLI 105

150 SLENTLHG 157
||| ||
106 CLEXT.HG 112

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Comparison of SEQ ID NO 2 - present application version SEQ ID NO 18
- US 2002/0123118

GAP of: check: 4547 from: 1 to: 387

readseq-39946_tmp_1 387 bp

to: check: 1233 from: 1 to: 102

readseq-51560_tmp_1 102 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
Length Weight: 2 Average Mismatch: -2.248

Quality: 142 Length: 387
Ratio: 1.392 Gaps: 0
Percent Similarity: 40.196 Percent Identity: 31.373

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
  :| ||||| | |. | | | : | . | |
1 .....MVTNVVDLRSDTVTXPSDAMRAAMAAADVDDDLXGADPTAH 41

51 RLEQTVARMAGKEAGLCVSGTSLNQIAIRTHLMQPPYSILCDYRAHVYT 100
  | | . | . |||| | | |||. | |. : | : : . | : :
42 RFEMEMAMITGKEAALFVPSGTMANLISVLVHCXXXGSEVILGDNSHIHI 91

101 HEAAGLAILSQAMVVPVPSNGDYLTLEDIKSHYVPDDGDIHGAPTRLIS 150
   : | . .
92 YXNGGXSTSAG..... 102

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Comparison of SEQ ID NO 2 - present application version SEQ ID NO 18
- US 2002/0123118

BESTFIT of: 13766.seq1.fas check: 4547 from: 1 to: 387

readseq-37479_tmp_1 387 bp

to: 13766.seq2.fas check: 1233 from: 1 to: 102

readseq-14526_tmp_1 102 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
Length Weight: 2 Average Mismatch: -2.248

Quality: 147 Length: 95
Ratio: 1.547 Gaps: 0
Percent Similarity: 43.158 Percent Identity: 33.684

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

13766.seq1.fas x 13766.seq2.fas

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11 ITAANDLRSDTFTTPTAEMMEAALEASIGDAVYGEDVDTVRLEQTVARMA 60
   :|  ||||| | |. | | | : | . | | | | . | .
2  VTNVVDLRSDTVTXPSDAMRAAMAAADVDDDLXGADPTAHRFEMEMAMIT 51

61 GKEAGLFCVSGTSLNQIAIRTHLMQPPYSILCDYRAHVYTHEAAG 105
   |||| || |||:.| |.: | : : .|:: : |
52 GKEAALFVPSGTMANLISVLVHCXXXGSEVILGDNShIHIYXNGG 96

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Comparison of SEQ ID NO 2 - present application version SEQ ID NO 20
- US 2002/0123118

2 versus 20

GAP of: check: 4547 from: 1 to: 387

readseq-51718_tmp_1 387 bp

to: check: 6883 from: 1 to: 67

readseq-20872_tmp_1 67 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
Length Weight: 2 Average Mismatch: -2.248

Quality: 134 Length: 387
Ratio: 2.000 Gaps: 0
Percent Similarity: 52.239 Percent Identity: 46.269

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

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1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
  :| ||||| || | | | :| |||
1 .....MVTRIVDLRSDTVTKPTEAMRAAMASAEVDDDLGYDPTAF 41
51 RLEQTVARMAGKEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYT 100
  ||| .|: |||| || |||: |
42 RLETEMAKTMGKEAALFVPSGTMGNL..... 67

```


Comparison of SEQ ID NO 2 - present application version SEQ ID NO 20
 - US 2002/0123118

BESTFIT of: 32550.seq1.fas check: 4547 from: 1 to: 387

readseq-26936_tmp_1 387 bp

to: 32550.seq2.fas check: 6883 from: 1 to: 67

readseq-46767_tmp_1 67 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
 CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
 Length Weight: 2 Average Mismatch: -2.248

Quality: 137 Length: 65
 Ratio: 2.108 Gaps: 0
 Percent Similarity: 53.846 Percent Identity: 47.692

Match display thresholds for the alignment(s):

| = IDENTITY
 : = 2
 . = 1

32550.seq1.fas x 32550.seq2.fas

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11 ITAANDLRSDTFTTPTAEMMEAALEASIGDAVYGEDVDTVRLEQTVARMA 60
   :|  ||||| | || | | : | | | | ||| .|:
  2 VTRIVDLRSDTVTKPTEAMRAAMASAEVDDVVLGYDPTAFRLETEMAKTM 51

61 GKEAGLFCVSGTSLN 75
   |||| || |||: |
52 GKEAALFVPSGTMGN 66
  
```

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 22
- US 2002/0123118

2 versus 22

GAP of: check: 4547 from: 1 to: 387

readseq-7457_tmp_1 387 bp

to: check: 8339 from: 1 to: 92

readseq-54326_tmp_1 92 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	145	Length:	387
Ratio:	1.576	Gaps:	0
Percent Similarity:	44.565	Percent Identity:	34.783

Match display thresholds for the alignment(s):

```

| = IDENTITY
: = 2
. = 1

```

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
  ||||| | | | | | | | | | | | | | | | | | | | | | |
1 .....MATKVVDLRSDTVTKPSEAMRAAMAAADVDDVVGADPTAC 41
51 RLEQTVARMAGKEAGLFCVSGTSLNQIAIRTHLMQPPYSILCDYRAHVYT 100
  | .||| ||| || |||:| |.: | : : .|::
42 RFXAEMARIMGKEAALFVPSGTMANLISVLAHCDARGSEVILGHDSHIHV 91
101 HEAAGLAILSQAMVVPVPSNGDYLTLEDIKSHYVPDDGDIHGAPTRLIS 150
  :
92 Y..... 92

```

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 22
 - US 2002/0123118

BESTFIT of: 12907.seq1.fas check: 4547 from: 1 to: 387

readseq-19879_tmp_1 387 bp

to: 12907.seq2.fas check: 8339 from: 1 to: 92

readseq-51164_tmp_1 92 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
 CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	147	Length:	90
Ratio:	1.633	Gaps:	0
Percent Similarity:	45.556	Percent Identity:	35.556

Match display thresholds for the alignment(s):

	=	IDENTITY
:	=	2
.	=	1

12907.seq1.fas x 12907.seq2.fas

```

12 TAANDLRSDTFTTPTAEMMEAALEASIGDAVYGEDVDTVRLEQTVARMA 61
   |  ||||| | |. | | | : | | | | | . ||. |
3  TKVVDLRSDTVTKPSEAMRAAMAAADVDDVVGADPTACRFXAEMARIM 52

62 KEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYTH 101
   ||| || |||:.| |.: | : : .|:: :
53 KEAALFVPSGTMANLISVLAHCDARGSEVILGHDSHIHVY 92
  
```

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 38
- US 2002/0123118

GAP of: check: 4547 from: 1 to: 387

readseq-52950_tmp_1 387 bp

to: check: 2915 from: 1 to: 343

readseq-11106_tmp_1 343 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
Length Weight: 2 Average Mismatch: -2.248

Quality: 334 Length: 398
Ratio: 0.974 Gaps: 9
Percent Similarity: 42.771 Percent Identity: 31.024

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
1 .....ARADPTAR 8
51 RLEQTVARMAGKEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYT 100
| :: .| : ||| || ||| : | :: | :: .| ::
9 RFQEEMAALMGKEAALFVPSGTMGNLVSVLAHCDVRGSEVILGDDSHIHL 58
101 HEAAGLAILSQAMVVPVPSNGDYLTLEDIKSHYVPDDGDIHGAPTRLIS 150
:| | :. | | .. : :: | . | | :: |||
59 YENGISTLGGVHPKTVRNNSDGTMDIDSIVAAIRPPGGGLYYPTTRLIC 108
151 LENT...LHGIVYPLEELVRIKAWCMENGLKLHCDGARIWNAQAQSGVPL 197
||| | | : : . ||| ||| ||| . |||
109 LENTHGNSGGKCLSAEYTEKVGEIAKSHGLKLHIDGARIFNASVALGVPV 158
198 KQYGEIFDSISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQGGGIRQS 247
. ||::||::|| :||:||||:|. | : || || |||.||
159 DRLVRAADSVSVCISKGLGAPVGSVIVGSKAFIDKAKILRKTLLGGGMRQV 208
248 GMMARMALVNINNDWKSQLLYSHSLAHELAE.YCEAKGIPLES.PA.DTNF 295
|. : | | : | . | | | | : . . . : | . ||
209 GVLCAAHVAV.RDNVGLADDDRKAKALADGLNKIEQFRVDSASVQTNM 257
296 VFINKAARMDPDVLVKKGLKYNV....KLMGGRVSFHYQVTRDTLEKV 340
||:: .|. . | . :|| |. |||. | |
258 VFLDIVDSRISSNKLCQVLGTHNVLASPRSPKSVRLVLHYQISDD...DV 304
341 KLAISEAFDYAKEHPDCNGPTQI.YRSESTEVDVDGNAIREIKTYKY 387
. |. : | | | | :: : . | . :
305 QYALT.CFKKAAEQLL..MGSTEHLAEQLLMGTTKNYSYQ..... 343

```

```

51  RLEQTVARMAGKEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYT 100
   | :: . | : ||| | | |||: | :: |      :: . :|
9   RFQEEMAALMGKEAALFVPSGTGMNLVSVLAHCDVRGSEVILGDDSHIHL 58
   . . . . .
101 HEAAGLAILSQAMVVPVVPNSGDYLTLEDIKSHYVDPDGDIGHAPTRLIS 150
   :| |:. | | | | | | | | | | | | | | | | | | | |
59  YENGGISLGGVHPKTVRNNSDGTMDIDSIVAAIRPPGGGLYPTTRLIC 108
   . . . . .
151 LENT...LHGIVYPLEELVRIKAWCMENGLKLHCDGARIWNAQAQSGVPL 197
   |||| | | | | | | | | | | | | | | | | | | | |
109 LENTHGNSSGGKCLSAEYTEKVGEIAKSHGLKLHIDGARIFNASVALGVPV 158
   . . . . .
198 KQYGEIFDSISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQQGGGIQRS 247
   . | | : | : | : | : | : | : | : | | | | | | | |
159 DRLVRAADSVSVCI SKGLGAPVGSVIVGSKAFIDKAKILRKTLLGGGMQV 208
   . . . . .
248 GMMARMALVNINNDWKSQLLYSHSLAHELAE.YCEAKGIPLESPA.DTNF 295
   |. : | | : | . | | | | | | | | | | | | | | |
209 GVLCAAHVAV.RDNVGLKADDRHKAKALADGLNKIEQFRVDSASVQTNM 257
   . . . . .
296 VFINKAARMDDPDLVKKGLKYNV....KLMGGRVSFHYQVTRDTLE 338
   ||:: . |. . |. . :| | | | | | | | | | | | | |
258 VFLDIVDSRISSNKLCQVLGTHNVLASPRSPKSVRLVLHYOISDDDDVO 305

```

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMEAALASIGDAVYGEDVDTV 50
      :| ||||| | | | :| ||| |
1 .....MVTNVVDLRSDVTVKPSDAMRAAMAAADVDDDLVGADPTAH 41
      .
51 RLEQTVARMAGKEAGLFCVSGTSLNQIAIRTHLMQPPYSILCDYRAHVYT 100
      || .||. |||| || |||:| |.: | :: .|:
42 RFEMEMARITGKEAALFVPSGTMANLISVLVHCDTRGSEVILGDNShiHI 91
      .
101 HEAAGLAILLSQAMVVPVVPNSGD.YLTLEDIKSHYVPDDGDIHGAPTRLI 149
      :| |: . : . |. | : :: | || :: |||
92 YENGGISITIG.GVHPKTVRNNPDGTMDDIDKIVVAIRHPDGALYYPTTRLI 140
      .
150 SLENT...LHGIVYPLEELVRKAWCMENGLKLHCDGARIWNAAAQSGVP 196
      |||| | | : . |||| ||||. ||. |||
141 CLENTHANC GGKCLSAEYTDVEGEVAKSHGLKLHIDGARIFNASVALGVP 190
      .
197 LKQYGEIFDSISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQGGGIRQ 246
      . . . ||:|:|:| :||:|:|:| |.: || || |. ||
191 VHRLVKAADSVSVCISKGLGAPVGSVIVGSTAFIEKAKILRKTLLGGMRQ 240
      .
247 SGMMARMALVNINNDWKSQLLYSHSLAHELAE.YCEAKGIPLESPA.DTN 294
      |: | | : | .| | | ||: . | .. . :||
241 VGILCAAAYVAV.RDTVGLADHRRRAKVLADGLKKIKHFRVDTTSVETN 289
      .
295 FVFINLKAARMDPDVLVKKGLKYNVKLM..GG...RVSFHYQVT....RD 335
      || :. .|. || | . . || | | |. |||:.
290 MVFFDIVDSRISPDKLCQVLEQRNVLAMPAGSKSMRLVIHYQISDSVDVQY 339
      .
336 TLEKVKLAISEAFDYAKEHPFDCNGPTQIYRSESETEVDVDGNAIREIKTY 385
      | |. | | |. . || |.
340 ALTCEKAAEEILTGSKKFEHLTNGTTRNSYGH..... 372

```

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 40
- US 2002/0123118

BESTFIT of: 15966.seq1.fas check: 4547 from: 1 to: 387

readseq-41171_tmp_1 387 bp

to: 15966.seq2.fas check: 5694 from: 1 to: 372

readseq-25287_tmp_1 372 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	439	Length:	368
Ratio:	1.244	Gaps:	9
Percent Similarity:	44.160	Percent Identity:	35.328

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

15966.seq1.fas x 15966.seq2.fas

```

11 ITAANDLRSDTFTTPTAEMMEAALEASIGDAVYGEDVDTVRLEQTVARMA 60
   :|  ||||| | | . | | | : | | | | | | | . ||
2  VTNVVDLRSDTVTKPSDAMRAAMAAADVDDVLGADPTAHRFEMEMARIT 51

61 GKEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYTHEAAGLAILS 110
   ||| | | ||| : | | : | | : | : | : | | : |
52 GKEAALFVPSGTMANLISVLVHCDTRGSEVILGDNSHIHIYENGISTIG 101

111 QAMVVPVVPVPSNGD.YLTLEDIKSHYVPDDGDIHGAPTRLISLENT...LH 156
    . | . | | : : | | | : | | | | | |
102 .GVHPKTVRNNPDGTMIDIKIVVAIRHPDGALYYPTTRLICLENTHANCG 150

157 GIVYPLEELVRIKAWCMENGLKLHCDGARIWNAAAQSGVPLKQYGEIFDS 206
   | | | : | | | | | | | | | | | | | | | |
151 GKCLSAEYTDDEVGEVAKSHGLKLHIDGARIFNASVALGVPVHRLVKAADS 200

207 ISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQQGGGIRQSGMMARMALV 256
   :| :| :| :| :| :| :| :| :| :| :| :| :| :| :|
201 VSVCIKGLGAPVGSVIVGSTAFIEKAKILRRTLGGGMRQVGILCAAAYV 250

257 NINNDWKSQLLYSHSLAELAE.YCEAKGIPLES.PA.DTNFVFINLKAAR 304
   : | | | | | | | | | | | | | | | | | | | |
251 AV.RDTVGLKADDHRRRAKVLADGLKKIKHFRVDTTTSVETNMVFFDIVDSR 299

305 MDPDVLVKKGLKYNVKLM..GG...RVSFHYQVT....RDTLEKVKLAIS 345
   . || | . . || | | | | . ||| : . . | | |
300 ISPDKLCQVLEQRNVLAMPAGSKSMRLVIHYQISDSQVYALTCVEKAAE 349

346 EAFDYAKEHPFDCNGPTQ 363
   | | . | . | | |
350 EILTGSKKFEHLTNGTTR 367

```

Comparison of SEQ ID NO 2 - present application version SEQ ID NO 42
- US 2002/0123118

GAP of: check: 4547 from: 1 to: 387

readseq-14212_tmp_1 387 bp

to: check: 1263 from: 1 to: 360

readseq-52153_tmp_1 360 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight: 8 Average Match: 2.778
Length Weight: 2 Average Mismatch: -2.248

Quality: 409 Length: 400
Ratio: 1.136 Gaps: 9
Percent Similarity: 45.821 Percent Identity: 34.006

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```

1 MTEFELPPKYITAANDLRSDTFTTPTAEMMEAALASIGDAVYGEDVDTV 50
  :| ||||| | | | | | : | | | |
1 .....MVTRIVDLRSDTVTKPTEAMRAAMASAEVDDDLGYDPTAF 41

51 RLEQTVARMAGKEAGLFCVSGTLSNQIAIRTHLMQPPYSILCDYRAHVYT 100
  ||| .|: |||| | |||: | :.: | :.: | :
42 RLETEMAKTMGKEAALFVPSGTMGNLVSVLVHCDVRGSEVILGDNCHINI 91

101 HEAAGLAILSQAMVVPVPSNGDYLTLE.DIKSHYVPDD.GDIHGAPTRL 148
  | |:| : | | | | |:| : | |:| : |:|
92 FENGGIATIGG..VHPRQVKNNDDGTIDIDLIEAAIRDPMGELFYPTTKL 139

149 ISLENT...LHGIVYPLEELVRIKAWCMENGLKLHCDGARIWNAQAQSGV 195
  | |||| | | | | : | | | | | | | | | | | |
140 ICLENTHANSNGRCLSVEYTDVRGELAKKHGLKLHIDGARIFNASVALGV 189

196 PLKQYGEIFDSISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQGGGIR 245
  | . . : | |:|:| | | | | |:|:| |:|:| | | | | | |
190 PVDRLVQAADSVSVCLSKGIGAPVGSVIVGSKNFIKARRLRKTLGGGMR 239

246 QSGMMARMALVNINNDWKSQLLYSHSLAHELAE.YCEAKGIPLES.PADT 293
  | |:| | | : . | | | | |:| | | : .: . :|
240 QIGLLCAAALVALQEN.VGKLES DHKKARLLADGLKEVKRLRVDAGSVET 288

294 NEVFFINL.KAARMDPDVLVKKGLKYNVKLMGG.....RVSFHYQVTRDTL 337
  | |||: . : : : | . : . | | | |:|: .
289 NMVFIDIEEGTKTRAEKICKYMEERGILVMQESSRMRVVLHHQISASDV 338

338 EKVKLAISEAFDYAKEHPFDCNGPTQIYRSESTEVDVDGNAIREIKTYKY 387
  : : | |
339 QYALSCFQQALAVKGVQNEMGN..... 360

```


Comparison of SEQ ID NO 2 - present application version SEQ ID NO 42
- US 2002/0123118

BESTFIT of: 23654.seq1.fas check: 4547 from: 1 to: 387

readseq-17620_tmp_1 387 bp

to: 23654.seq2.fas check: 1263 from: 1 to: 360

readseq-6893_tmp_1 360 bp

Symbol comparison table: /applications1/gcg/share/matrix/blosum62.cmp
CompCheck: 1102

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	426	Length:	298
Ratio:	1.464	Gaps:	7
Percent Similarity:	49.653	Percent Identity:	38.194

Match display thresholds for the alignment(s):

```

| = IDENTITY
: = 2
. = 1

```

23654.seq1.fas x 23654.seq2.fas

```

11 ITAANDLRSDTFTTPTAEMMEAALEASIGDAVYGEDVDTVRLEQTVARMA 60
   :|  |||||  ||  |  |  |  |  |  |  |  |  |  |  |  |  |  |
2  VTRIVDLRSDTVTKPTEAMRAAMASAEVDDDLGYDPTAFRLETEMMAKTM 51

61 GKEAGLFCVSGTILSNQIAIRTHLMQPPYSILCDYRAHVYTHEAAGLAILS 110
   ||||  ||  |||:  |::  |  |  |  |  |  |  |  |  |  |  |
52 GKEAALFVPSGTMGNLVSVLVHCDVRGSEVILGDNCHINIFENGGIATIG 101

111 QAMVVPVVPVPSNGDYLTLTLE.DIKSHYVPDD.GDIHGAPTRLISLENT...L 155
    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
102 G..VHPRQVKNNDDGTIDIDLIEAAIRDPMGELFYPTTKLICLENTHANS 149

156 HGIVYPLEELVRIKAWCMENGLKLHCDGARIWNAAAQSGVPLKQYGEIFD 205
    |  .|  |:  ..|||  ||||.  ||.  |||.  .  :  |
150 GGRCLSVEYTDVRGELAKKHGLKLHIDGARIFNASVALGVPVDRLVQAAD 199

206 SISICLSKSMGAPIGSVLVGNLKFVKKATHFRKQGGGIRQSGMMARMAL 255
   |:|:|  |||  .|||:|  ||.  |:  ||  ||  |||.  ||  |:  ||
200 SVSVCLSKGIGAPVGSVIVGSKNFIAKARRLRKTLGGGMRQIGLLCAAAL 249

256 VNINNDWKSQLLYSHSLAHELAE.YCEAKGIPLES.PADTNFVFINLK 301
   |  :  .  .|  |  |  ||:  |  |  :  :.  :||  |||.  .
250 VALQEN.VGKLESDHKKARLLADGLKEVKRLRVDAGSVETNMVFDIE 296

```